Canadian Consensus Conference on Dementia
2012
Conférence Canadienne Consensuelle sur la Démence

cccdtd4
Faculty/Presenter Disclosure

• Faculty: C. Patterson

• Relationship with commercial interests:
  - Grants/Research Support: CIHR, Heart & Stroke Foundation
  - Speakers Bureau/Honoraria: Nil
  - Consulting Fees: Nil
  - Other: In-kind support from Hamilton Health Sciences
• Canadian Consensus Conference on Assessment of Dementia (CCCAD) 1989
• Canadian Consensus Conference on Dementia 1999
• 3rd Canadian Consensus Conference on Diagnosis and Treatment of Dementia (cccdtd3) 2006
• 2012 Canadian Consensus Conference on Dementia (cccdtd4)
Reason for 2012 CCCD

• New definitions and conceptualization of AD
• Availability of biomarkers (e.g. CSF)
• New neuroimaging techniques (e.g. amyloid and functional MRI neuroimaging)
• Ethical concerns about clinical use (misuse) of biomarkers
• Target audience: non dementologist specialists, FMDs
Steering Committee

- Christopher Patterson (Co-Chair)
- Serge Gauthier (Co-Chair)
- Howard Chertkow
- Michael Gordon (Ethics consultant)
- Pedro Rosa-Neto
- Ken Rockwood (CDKTN)
- Jean-Paul Soucy
• Posting background papers to website
• Comments added on line
• Voting online
• Advanced dissemination strategy (Alzheimer’s & Dementia journal)

• Adherence to AGREE template
• Use of GRADE evidence classification
• Advanced knowledge translation strategy (DKTN, publications, web based)
AGREE Collaboration (Appraisal of Guidelines, research and Evaluation)

1. Scope and purpose: specific statement & description target population
2. Stakeholder involvement
3. Rigour of development: search strategy, criteria for selecting evidence, linkage to recommendations, external review
4. Clarity and presentation
5. Applicability: organization, cost, monitoring
6. Editorial independence: isolation from funding sources, conflict of interest declaration

Qual Saf Health Care 2003 12:18-23
GRADE: *Strong* evidence “We recommend...”

<table>
<thead>
<tr>
<th>Grade of recommendation</th>
<th>Benefits vs. risks &amp; burdens</th>
<th>Methodological quality of supporting evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong recommendation, high quality evidence 1A</td>
<td>Desirable effects clearly outweigh undesirable effects (or vice versa)</td>
<td>Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies</td>
</tr>
<tr>
<td>Strong recommendation, moderate quality evidence 1B</td>
<td>Desirable effects clearly outweigh undesirable effects (or vice versa)</td>
<td>Evidence from RCTs with important limitations or very strong evidence from observational studies</td>
</tr>
<tr>
<td>Strong recommendation, low or very low quality evidence 1C</td>
<td>Desirable effects clearly outweigh undesirable effects (or vice versa)</td>
<td>Evidence for at least one critical outcome from observational studies, case series, RCTs with serious flaws or indirect evidence</td>
</tr>
</tbody>
</table>
**GRADE: Weak evidence “We suggest…”**

<table>
<thead>
<tr>
<th>Grade of recommendation</th>
<th>Benefits vs. risks &amp; burdens</th>
<th>Methodological quality of supporting evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weak recommendation, high quality evidence 2A</td>
<td>Desirable effects closely balanced with undesirable effects</td>
<td>Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies</td>
</tr>
<tr>
<td>Weak recommendation, moderate quality evidence 2B</td>
<td>Desirable effects closely balanced with undesirable effects</td>
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</table>
Process for achieving consensus:
Electronic voting already recorded

• Consensus = 80% of CCCD participants
• Partial consensus = 60-79%
• Recommendation may be amended
• Less than 60%: option to drop or rewrite recommendation, opposing view
• Recommendations may be subsequently abbreviated for clarity
Definitions

H. Chertkow, H. Feldman, C. Jacova, F. Massoud
Definitions

We recommend the adoption of the criteria for dementia proposed by the 2011 NIA-AA working group.

We recommend the adoption of the recommendations concerning probable and possible Alzheimer’s Disease dementia core clinical diagnostic criteria proposed by the 2011 NIA-AA working group.

We recommend the adoption of the core clinical criteria for MCI proposed by the 2011 NIA-AA working group.

We recommend the 2011 ASA/AHA recommendations for the diagnosis of VCI.
Dementia (NIA-AA)
is diagnosed when there is cognitive or behavioural symptoms which:
1. Interfere with function at work or usual activities
2. Represent a decline from previous function
3. Are not explained by delirium or major psychiatric disorder
4. Cognitive impairment is detected by:
   (a) history (person and knowledgeable informant)
   (b) mental status or bedside neuropsychological testing
5. The cognitive or behavioural impairment involves a minimum of 2 of the following domains
   (a) memory
   (b) reasoning, handling complex tasks, judgment
   (c) impaired visuospatial function
   (d) language
   (e) changes in personality behaviour or comportment

McKhann G et al. Alzheimer’s and Dementia 2011; 7: 263
Alzheimer’s disease (probable) NIA-AA

- Dementia
- Insidious onset
- Clear cut history of worsening
- Initial and prominent cognitive deficits on history and examination in one of:
  (a) amnestic presentation
(b) non amnestic presentation
   language (PNFA)
   visuospatial (PCA)
   executive

Not probable AD if:
• Substantial evidence of cerebrovascular disease
• Core features of LBD
• Prominent features of Bv FTD
• Prominent features of semantic dementia or PPA
• Other neuro or non neuro illness or drugs

McKhann G et al Alz Dement 2011; 7: 263
MCI-clinical criteria NIA-AA

- Concern regarding a change in cognition (individual or observer)
- Impairment in one or more cognitive domains (typically 1-1.5 SD below)
- Preservation of independence in functional activities
- Not demented
- (Visual & language variants)

Albert M et al Alz Dement 2011; 7: 270
Vascular Cognitive Impairment: Probable VaD (NIA-AA)

- Dementia
- The deficits in ADL are independent of the motor/sensory sequelae of the vascular event.
- There is no history of gradually progressive cognitive deficits before or after the stroke that suggests the presence of a nonvascular neurodegenerative disorder.

Vascular Cognitive Impairment: Probable VaD

- There is cognitive impairment and imaging evidence of cerebrovascular disease and

- (a) There is a clear temporal relationship between a vascular event (e.g. clinical stroke) and onset of cognitive deficits, or

- (b) There is a clear relationship in the severity and pattern of cognitive impairment and the presence of diffuse, subcortical cerebrovascular disease pathology (e.g. as in CADASIL).

Research recommendation:

We recommend the IWG definition of “asymptomatic at-risk for AD” states for research purpose.

We recommend reassessment of the utility of the concept of prodromal AD in the future when AD-PP biomarkers are available, validated, and ready for use in Canada.
A new lexicon of Alzheimer’s Disease (IWG)

<table>
<thead>
<tr>
<th>Condition</th>
<th>AD diagnosis</th>
<th>Presence of impairment on specified memory tests</th>
<th>Evidence of biomarkers in vivo</th>
<th>Additional requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical AD</td>
<td>Yes</td>
<td>Required</td>
<td>Required</td>
<td>None</td>
</tr>
<tr>
<td>Atypical AD</td>
<td>Yes</td>
<td>Not required</td>
<td>Required</td>
<td>Specific clinical presentation</td>
</tr>
<tr>
<td>Prodromal AD</td>
<td>Yes</td>
<td>Required</td>
<td>Required</td>
<td>Absence of dementia</td>
</tr>
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<td>AD dementia</td>
<td>Yes</td>
<td>Required</td>
<td>Required</td>
<td>Presence of dementia</td>
</tr>
<tr>
<td>Mixed AD</td>
<td>Yes</td>
<td>Required</td>
<td>Required</td>
<td>Evidence of comorbid disorders</td>
</tr>
<tr>
<td>Preclinical AD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic at risk for AD</td>
<td>No</td>
<td>Not present</td>
<td>Required</td>
<td>Absence of symptoms of AD</td>
</tr>
<tr>
<td>Presymptomatic AD</td>
<td>No</td>
<td>Not present</td>
<td>Not required</td>
<td>Absence of symptoms of AD and presence of monogenic AD mutation</td>
</tr>
<tr>
<td>Mild cognitive impairment</td>
<td>No</td>
<td>Not required</td>
<td>Not required</td>
<td>Absence of symptoms or biomarkers specific for AD</td>
</tr>
</tbody>
</table>

AD=Alzheimer’s disease.

Table 2: Comparative features of the different conditions described in the new lexicon according to the new research criteria framework.

Dubois B et al. Lancet Neurol 2010; 9: 1118
A new lexicon of Alzheimer’s Disease (IWG)

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*Table 2: Comparative features of the different conditions described in the new lexicon according to the new research criteria framework*

Dubois B et al. Lancet Neurol 2010; 9: 1118
Theoretical changes of biomarkers in AD

Sperling R et al Alz Dement 2011
Amyloid Imaging
with PiB (Pittsburg compound B)
Florbetapir now approved by FDA
Definitions

Given that the presence of brain amyloid in normal people is of uncertain significance, the CCCD discourages the use of amyloid imaging in individuals without memory loss, outside of the research setting.

The medical community should be clear in its discussions with patients, the media and the general population that presence of brain amyloid in normal people is of unclear significance at the present time.
Neuroimaging

J-P Soucy, R. Bartha, C. Bocti,
M. Borrie, A. Burhan, R. LaForce,
P. Rosa-Neto
Neuroimaging: Structural imaging: CT & MRI

For the assessment of a person with cognitive impairment, at least one structural imaging procedure (CT or MRI of the brain) is recommended to establish the presence of clinically unsuspected cerebrovascular disease and to rule out potentially reversible structural etiologies. (Grade 1B)

We suggest that a head MRI is preferred when a radiologist/neuroradiologist and/or a cognitive specialist (neurologist, geriatrician, or geriatric psychiatrist) can interpret patterns of atrophy and other features that may provide added diagnostic and predictive value as deemed appropriate by the specialist. (Grade 2B)
Neuroimaging: New indication for structural imaging: CT & MRI

In addition to previously listed indications for structural imaging, a CT or MRI should be done in the assessment of a person with cognitive impairment if the presence of unsuspected cerebrovascular disease would change the clinical management.
Neuroimaging: Structural imaging: CT & MRI

**Standardization** of clinical acquisition of core MRI dementia sequences is recommended in Canadian centres that have radiologists and cognitive specialists with expertise in assessing cognitive disorders, particularly when repeat MRI images can provide additional diagnostic, prognostic and safety information. (Grade 1B).

We suggest that when available in the clinic, cognition specialists may use the computer images of the brain to educate a person with cognitive impairment and family members about changes in the brain. This knowledge may reinforce adherence to vascular risk factor management and to lifestyle modification to improve brain health. (Grade 2C).

<table>
<thead>
<tr>
<th>For</th>
<th>All</th>
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<tbody>
<tr>
<td>73.3% (11)</td>
<td>26.7% (4)</td>
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</table>
For a patient with a diagnosis of dementia who has undergone the recommended baseline clinical and structural brain imaging evaluation and who has been evaluated by a dementia specialist but whose underlying pathological process is still unclear, preventing adequate clinical management, we recommend that the specialist obtain a 18F-FDG PET scan for differential diagnosis purposes (Grade 1B).

For a patient with a diagnosis of dementia who has undergone the recommended baseline clinical and structural brain imaging evaluation and who has been evaluated by a dementia specialist but whose underlying pathological process is still unclear, preventing adequate clinical management, and who cannot be practically referred for an 18F-FDG PET scan, we recommend that a SPECT rCBF study be performed for differential diagnosis purposes (Grade 2C).
Neuroimaging: FDG PET & SPECT

For a patient with MCI evaluated by a dementia specialist and in whom clinical management would be influenced by evidence of an underlying neurodegenerative process, we suggest that an 18F-FDG PET scan be performed or, if not available, that a SPECT rCBF study be performed (Grade 2C).

For 72.2% (13)
Against 22.2% (4)
One abstention (5.5%)

For a patient with a diagnosis of dementia who has undergone the recommended baseline evaluation and who has been evaluated by a specialist but whose underlying pathological process is still undefined, and in whom 18F-FDG PET or SPECT rCBF imaging have not provided a satisfactory answer, we suggest that 131I-MIBG cardiac imaging be performed if differentiating between DLB or PD associated dementia and AD is needed for management purposes (evidence level: C).

For 22.2% (4)
Against 61% (11)
3 abstentions (16.7%)
We recommend that standardized acquisition/interpretation protocols for both 18F-FDG PET and SPECT rCBF imaging in subjects with suspected neurodegenerative conditions be defined.
Neuroimaging: FDG PET & SPECT

Research recommendation:

We suggest that 18F-FDG PET and SPECT rCBF imaging be used for enriching populations of controls and affected patients in therapeutic protocols evaluating the efficacy of dementia course-altering medications.

Research recommendation:

We recommend that protocols for obtaining approval for clinical use of SPECT/PET markers of striato-nigral fibers integrity for application to the differential diagnosis of AD/DLB be launched.
At present, there is no clinical indication for amyloid imaging in cognitively normal individuals, initial investigation of cognitive complaints, differentiating AD from other Aβ-associated dementia (e.g. DLB, CAA), differentiating between AD clinical variants (e.g. classic amnestic AD vs. PCA or lvPPA), and differentiating between non-AD causes of dementia (e.g. molecular subtypes of FTLD).
Neuroimaging: Amyloid Imaging

Amyloid imaging is not currently approved in Canada. Should amyloid imaging become available in Canadian clinicians in the future, *it must not be considered a routine test and we recommend it as an adjunct to a comprehensive evaluation for complex atypical presentations in referral to tertiary care Memory Clinics when a more accurate clinical diagnosis is needed* (Grade 1B).
Neuroimaging: Amyloid Imaging

Should this technique become available to Canadian clinicians in the future, we recommend against its use in cognitively normal individuals or initial investigation of cognitive complaints (Grade 1B).

When faced with amyloid test results obtained outside Canada, physicians should be very cautious in their interpretation, i.e. used in isolation this test cannot diagnose AD, MCI, or differentiate normal from abnormal aging, and we recommend they consult with a dementia specialist familiar with this technique.
Neuroimaging: Amyloid Imaging

Although amyloid imaging represents a promising technique in the evaluation of dementia, there are many unknowns that could impact on its diagnostic utility and therefore we recommend that its use be restricted to research at present (Level 1C).

Health Policy recommendation:

Based on current evidence we recommend that Health Canada approves the use of amyloid imaging in tertiary care dementia clinics.

<table>
<thead>
<tr>
<th>For</th>
<th>Against</th>
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<tbody>
<tr>
<td>All</td>
<td></td>
</tr>
<tr>
<td>63% (12)</td>
<td>37% (7)</td>
</tr>
</tbody>
</table>
Neuroimaging: Amyloid imaging

**Research recommendation:**

Testing and longitudinal follow-up of asymptomatic individuals or patients with subjective cognitive impairments not meeting MCI criteria, or at-risk individuals (e.g. gene mutation carriers, family history of AD, ApoE ε4) should be restricted to research;

**Research recommendation:**

Future research should explore (1) the natural evolution of amyloid burden and its role in the pathophysiology of AD and other dementias, (2) its use as a potential surrogate marker for anti-amyloid therapies, (3) the value of new 18F amyloid tracers, (4) perform PETpathology correlations, and (5) compare amyloid imaging with CSF AD biomarkers as well as downstream markers of degeneration.
Neuroimaging: Amyloid Imaging

Research recommendation:

In research settings with amyloid imaging capabilities, investigators should be encouraged to develop projects that further validate the clinical and research uses of this technique and evaluate its readiness for translation to clinical care;

Research recommendation:

Trial designers are strongly encouraged to use this technique to (1) decrease the heterogeneity of their MCI population; (2) identify a cohort that is likely to respond to a drug with anti-amyloid properties; and (3) study patients that are likely to convert to AD in a relatively short time frame;
Neuroimaging: Functional MRI

We recommend against the use of Functional MRI for the clinical investigation of patients presenting with cognitive complain (Grade1B)

Research recommendation:

Future studies should use standardized acquisition of images protocol and experimental paradigm to allow pooling of data. (Grade1C)

Research recommendation:

Future studies with large number of participants and longer period of follow-up are needed to allow firm conclusions on the value of fMRI in early detection of dementia and on predicting conversion of MCI to AD (Grade1B)
Neuroimaging: Functional MRI

**Research recommendation:**
Future studies with large number of participants and longer period of follow-up are needed to allow firm conclusions regarding the value of fMRI in distinguishing between AD and non-AD dementia such as FTD and LBD (Recommendation level 1, evidence level B)

**Research recommendation:**
Future studies with large number of participants and longer period of follow-up are needed to allow firm conclusions on the value of fMRI in assessing changes in brain activation in response to intervention such as cognitive training and pharmacotherapy (Recommendation level 1, evidence level C)
Neuroimaging: Functional MRI

Research recommendation:

Future studies with large number of participants and longer period of follow-up are needed to allow firm conclusions on the value of fMRI mapping brain activation in various neuropsychiatric and behavioural symptoms in the context of pre-clinical and clinical dementia such as depression, apathy and psychosis, which will help in developing specific treatments for these symptoms. (Grade 2C)
Neuroimaging: MR Spectroscopy

Magnetic resonance spectroscopy shows promise for predicting which people with mild cognitive impairment are likely to progress to dementia. However, it is not currently recommended for clinical use to make or differentiate a diagnosis of dementia in people presenting with mild cognitive impairment (Grade 2C).

1H MRS remains a promising technique for the identification of subjects with mild cognitive impairment who will convert to dementia. Further multi-site longitudinal studies should be conducted to establish normative values. Such studies should utilize standardized enrollment criteria, diagnosis criteria, data acquisition methods, and include automated analysis of spectra that incorporates proper prior knowledge of metabolite line shapes.

For

All

93.8% (15)  6.3% (1)
Neuroimaging: MR Spectroscopy

Standardized 1H MRS data acquisition and analysis methods should be developed in co-ordination with recommendations from the International Society of Magnetic Resonance in Medicine.

Future 1H MRS studies to demonstrate clinical effectiveness should utilize 3 Tesla MRI where available to increase data quality.
Neuroimaging: Other Markers

Imaging biomarkers of neuroinflammation or Tau pathology in dementia patients are not recommended in clinical practice.

Although there is a growing body of literature supporting the use of dopamine presynaptic imaging agents for differentiating Lewy Body from AD disease, these imaging agents are not yet recommendable for clinical practice.
Liquid biomarkers

P.Rosa-Neto, G-Y R.Hsiung, M. Marsellis
Liquid Biomarkers

Plasma $\text{A}\beta$ 1-42 levels are not recommended for clinical practice.

Measures of CSF $\text{A}\beta$ 1-42, total tau and phosphorylated tau at ser 181 are recommended for the biomarker workup of patients with atypical dementia.

Measures of CSF $\text{A}\beta$ 1-42, total tau and phosphorylated tau at ser 181 should be collected following a specific protocol and the quantification must be carried out by an experienced lab with a validated technology and continuous participation in quality control programs.
Early Onset Dementia

S. Gauthier, D. Sadovnick, S. Black, G-Y R. Hsiung, M. Masellis, S. Prasad, M. Williams, P. Rosa-Neto
Early Onset Dementia

All patients with early onset dementia should be referred to a memory clinic, preferably one with access to genetic counselling and testing when appropriate.

The cost of genetic counselling and testing should be covered by public funding.

Physicians should be sensitive to the special issues associated with early onset dementia, particularly in regard to loss of employment and access to support services appropriate for that age group.
Early Onset Dementia

Research recommendations

Considering the rarity of early onset dementia, a national registry for interested at risk individuals, mutation carriers and symptomatic patients will facilitate therapeutic research.

88.9% (16)  11.1% (2)

Health Policy recommendation:

This registry should be supported by public funding.

83.3% (15)  16.7% (3)
Rapidly Progressive Dementia

C. Patterson, A. Rashed, G. Heckman, J. Crowson
Rapidly Progressive Dementia

It is suggested that RPD be defined as a dementia which develops within 12 months after the appearance of first cognitive symptoms. (Grade 2C)

94.1% (16)  5.9% (1)

It is suggested that individuals suspected of RPD be referred to physicians who are experienced and have access to the diagnostic facilities able to mount an organized and comprehensive diagnostic procedure. (Grade 2C)

94.1% (16)  5.9% (1)

After exclusion of delirium and evident underlying causes of RPD, it is suggested that a diagnostic strategy for RPD be based on the prevalence of causes of RPD in case series. (Grade 2B)

All
Rapidly Progressive Dementia

The diagnostic strategy should emphasize the detection of potentially curable conditions, such as infections, immune mediated and toxic metabolic causes. Table 6 outlines such an approach. (Grade 2B)

For individuals with AD, it is suggested that a decline of 3 or more points on the MMSE in 6 months, which identifies a group with a worse prognosis, is a signal to explore comorbid conditions and review pharmacological management. (Grade 2B)

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>94.1% (16)</td>
<td>5.9% (1)</td>
</tr>
<tr>
<td>All</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Suggested approach to RPD

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Tests to be conducted on all RPD patients</th>
<th>Additional tests to consider</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>Onset, duration, associated features, concomitant conditions, exposures (tobacco, industrial chemicals, heavy metals, alcohol); complete medication review; past history and symptoms of systemic disease; travel history, sexual, recreational drug or blood products exposure; collateral history from close relatives; hallucinations, psychosis; fluctuating presentation; family history; headache; weight loss; skin rashes, etc.</td>
<td>Collateral history from other sources; previous hospital admissions, other physicians, workplace, other relatives; search for evidence of cognitive “normality” at previous points in time.</td>
</tr>
<tr>
<td>Examination</td>
<td>Signs of systemic disease (any system, especially cardiovascular, pulmonary, GI, skin, rheumatological), optic fundi, neurological examination for focal signs, rigidity, motor disorders, cerebellar signs, myoclonus; physically examine all medications; cognitive testing</td>
<td>Full neuropsychological testing.</td>
</tr>
</tbody>
</table>
| Laboratory | CBC, routine chemistry, Se. E12, Calcium, TSH, electrolytes, ISF, ANA, CRP | HIV, VDRL, vasculitis screen, anti-thyroglobulin and anti-

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<tr>
<td>Imaging</td>
<td>MRI with and without contrast; FLAIR and DWI; Chest X-Ray</td>
<td>MR angiogram, CT chest, abdomen, pelvis; PET scanning (e.g. FDG, florbetapir [only available in research settings]).</td>
</tr>
<tr>
<td>CSF</td>
<td>Protein, glucose, IgG, VDRL, oligoclonal banding, cell count and differential</td>
<td>Cultures (bacterial including AFB; fungal) viral studies, protein 14-3-3, PS 100, cytology, Whipple PCR, Lyme serology, [amyloid β 1-42], total and phosphorylated tau may be available in some research settings.</td>
</tr>
<tr>
<td>EEG</td>
<td>Standard EEG</td>
<td></td>
</tr>
<tr>
<td>Brain biopsy</td>
<td>Biopsy when diagnosis is essential and all above procedures have failed to establish diagnosis</td>
<td></td>
</tr>
</tbody>
</table>

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Update on Pharmacological Treatment

N. Herrmann, K. Lanctôt, D. Hogan
Many cases of dementia have more than one condition contributing to causation. Most commonly this will be a combination of Alzheimer’s disease with other brain pathology. We recommend that management be based on what is (are) felt to be the predominant contributing cause(s). (Grade 1B)

We recommend cholinesterase inhibitors as a treatment option for Alzheimer’s disease with cerebrovascular disease. (Grade 1B)
Update on Pharmacological Treatment

Cholinesterase inhibitors are recommended as a treatment option for dementia associated with Parkinson’s disease. (Grade 1A)

All three cholinesterase inhibitors have demonstrated efficacy for mild to severe AD. We recommend a trial of a ChEI for most patients with AD. (Grade1A)

There is insufficient and inconsistent evidence on which to make a recommendation either for or against the use of the currently available cholinesterase inhibitors for the treatment of probable or possible vascular dementia. (Grade 2B)

All
### Update on Pharmacological Treatment

Direct comparisons do not suggest differences between cholinesterase inhibitors (Grade 2B). Selection of agent will be based on adverse effect profile, ease of use, familiarity, and differences between the agents in their pharmacokinetics and other mechanisms of action.

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<td>94.1% (16)</td>
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Combination therapy of a cholinesterase inhibitor and memantine is rational (as the medications have different mechanisms of action) and appears to be safe, but there is insufficient evidence to recommend for or against this combination (Grade 2B)
DOMINO study: donepezil and memantine in mod/severe AD

Figure 3. Mean Scores on the Standardized Mini–Mental State Examination (SMMSE) and the Bristol Activities of Daily Living Scale (BADLS), According to Visit Week and Treatment Group.

Scores on the SMMSE range from 0 to 30, with higher scores indicating better cognitive function; scores on the BADLS range from 0 to 60, with higher scores indicating greater impairment. Shown are raw estimates of the mean score at each visit. Error bars denote the standard error.

Update on Pharmacological Treatment

Discontinuing cholinesterase inhibitors in patients with moderate to severe Alzheimer’s disease may lead to worse cognitive function and greater functional impairment as compared to continued therapy (Level 2B). This must be balanced with the risk for known side-effects and drug costs if therapy continues. It is suggested that cholinesterase inhibitors be discontinued when:

a) The patient and/or their proxy decision maker decide to stop after being appraised of the risks and benefits of continuation and discontinuation
b) The patient is sufficiently non-adherent with the medication that continued prescription of it would be useless, and it is not possible to establish a system for the administration of the medication to rectify the problem;
c) The patient’s rate of cognitive, functional, and/or behavioural decline is greater on treatment compared to that prior to being treated;
d) The patient experiences intolerable side effects that are definitely or probably related to the cholinesterase inhibitor;
e) The comorbidities of the patient make continued use of the agent either unacceptably risky or futile (e.g., terminally ill); or,
f) The patient's dementia progresses to a stage (e.g., Global Deterioration Scale stage 7) where there would be no clinically meaningful benefit from continued therapy.
Update on Pharmacological Treatment

When a decision has been made to discontinue therapy because of a perceived lack of effectiveness, it is suggested that the dose be tapered before stopping the agent and that the patient be monitored over the next 1-3 months for evidence of an observable decline. If this occurs, it is suggested that consideration be given to reinstating therapy. (Level 2C)

If the patient had an inadequate response to non pharmacological interventions or has a major affective disorder, severe dysthymia, or severe emotional lability, we recommend that a trial of an antidepressant could be considered. (Grade 2A)
Update on Pharmacological Treatment

Based on good evidence we recommend that valproate should *not* be used for agitation and aggression in AD (Grade 1A)

There is no good evidence to recommend for or against the use of cholinesterase inhibitors and/or memantine for the treatment of neuropsychiatric symptoms as a primary indication (Grade 2B)

For All

For All
Update on Pharmacological Treatment

We suggest that risperidone, olanzapine and aripiprazole be used for severe agitation, aggression and psychosis associated with dementia where there is risk of harm to the patient and/or others. The potential benefit of all antipsychotics must be weighed against the significant risks such as cerebrovascular adverse events and mortality. (Grade 2A)
Update on Pharmacological Treatment

There is insufficient evidence to recommend for or against the use of quetiapine in the management of severe agitation, aggression and psychosis associated with dementia (Grade 2B)

There is insufficient evidence to recommend for or against the use of SSRIs or trazodone in the management of agitated patients. (Grade 2B)
Dissemination and Knowledge Translation

Preplanned journal strategy
CDKTN
Health Plexus
Other
CLINICAL PRACTICE GUIDELINES/CONSENSUS STATEMENTS

Recommendations of the 4th Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCCDT4)

Sage Geddes, MD, Christopher Patterson, MD, Howard Sheps, MD, Michael Hunter, MD, Martin Herman, MD, Kenneth Rosow, MD, Peter Beekley, MD, PhD, and Paul Seabrook, MD, on behalf of the CCCDT4 participants.

ABSTRACT

The 4th CCCDT4 conference May 2012 in Montreal with the primary aim of updating the previous diagnostic and treatment guideline of Alzheimer’s Disease (AD) and related dementias (CDS). TheCCCDS4 recommendations build on the evidence for the use of non-pharmacological therapies, the evidence for the use of pharmacological therapies, and the evidence for the use of cerebral amyloid angiopathy. The conference also identified emerging research in the field of Alzheimer’s disease and related dementias. The guidelines were developed through a systematic review of the literature and included input from experts in the field. The guidelines were approved by all members of the conference and are intended to be used by primary care physicians, family physicians, and other healthcare providers who care for patients with AD and related dementias.

METHODS

The conference was attended by 70 participants from across Canada and the United States. The conference was held at the Intercontinental Hotel in Montreal, Quebec, Canada. The conference aimed to bring together experts in the field of Alzheimer’s disease and related dementias to discuss the latest research and best practices in the management of these conditions. The conference was organized by the Canadian Medical Association (CMA) and the Alzheimer Society of Canada (ASC). The conference was funded by the CMA and the ASC. The conference was open to all healthcare providers who care for patients with AD and related dementias.

4th Canadian Consensus Conference on the Diagnosis and Treatment of Dementia

Sage Geddes, MD, Christopher Patterson, MD, Howard Sheps, MD, Michael Hunter, MD, Martin Herman, MD, Kenneth Rosow, MD, Peter Beekley, MD, PhD, and Paul Seabrook, MD, on behalf of the CCCDT4 participants.

On May 30, 2012, in Montreal, the 4th Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCCDT4) was held to update guidelines for the diagnosis and treatment of Alzheimer’s disease (AD) and related dementias. The conference was organized by the Canadian Medical Association (CMA), in collaboration with the Alzheimer Society of Canada (ASC). The conference was held at the Intercontinental Hotel in Montreal, Quebec, Canada. The conference was attended by 70 participants from across Canada and the United States. The conference aimed to bring together experts in the field of Alzheimer’s disease and related dementias to discuss the latest research and best practices in the management of these conditions. The conference was funded by the CMA and the ASC. The conference was open to all healthcare providers who care for patients with AD and related dementias.

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The guidelines presented at the conference were developed through a systematic review of the literature and included input from experts in the field. The guidelines were approved by all members of the conference and are intended to be used by primary care physicians, family physicians, and other healthcare providers who care for patients with AD and related dementias.

In conclusion, the 4th Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCCDT4) was held to update guidelines for the diagnosis and treatment of Alzheimer’s disease (AD) and related dementias. The conference was organized by the Canadian Medical Association (CMA) and the Alzheimer Society of Canada (ASC). The conference was held at the Intercontinental Hotel in Montreal, Quebec, Canada. The conference was attended by 70 participants from across Canada and the United States. The conference was funded by the CMA and the ASC. The conference was open to all healthcare providers who care for patients with AD and related dementias.
Alzheimer’s Research and Therapy

2 special issues containing most of the articles developed from the background papers

Canadian Family Physician
CME based on cccdtld4
What's New from the Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCCDTD4)
Summary

• Emergence of CSF and neuroimaging biomarkers have prompted new recommendations for clinical practice
• Clinical definitions are little changed
• Few new pharmacological recommendations (valproate, memantine)
• EOD and RPD recommendations
• Extensive research agenda
Differential risk of death associated with antipsychotics

Huybrechtsk K et al BMJ Feb 23. 344.e977
Differential risk of death associated with antipsychotics

Huybrechtsk K et al BMJ Feb 23. 344.e977
Mortality risk with antipsychotics

30,000 DVA over age 65 with dementia

<table>
<thead>
<tr>
<th>Exposure Analysis</th>
<th>Adjusted, Unweighted</th>
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<tbody>
<tr>
<td>Risperidone</td>
<td>1.00</td>
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<tr>
<td>Haloperidol</td>
<td>1.59 1.36–1.85 &lt;0.0001</td>
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<tr>
<td>Olanzapine</td>
<td>1.06 0.93–1.22 0.3954</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>0.74 0.65–0.83 &lt;0.0001</td>
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</table>

### MCI criteria incorporating biomarkers

<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>Biomarker probability of AD etiology</th>
<th>Aβ (PET or CSF)</th>
<th>Neuronal injury (tau, FDG, sMRI)</th>
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</thead>
<tbody>
<tr>
<td>MCI—core clinical criteria</td>
<td>Uninformative</td>
<td>Conflicting/indeterminant/untested</td>
<td>Conflicting/indeterminant/untested</td>
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<tr>
<td>MCI due to AD—intermediate likelihood</td>
<td>Intermediate</td>
<td>Positive</td>
<td>Untested</td>
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<tr>
<td></td>
<td></td>
<td>Untested</td>
<td>Positive</td>
</tr>
<tr>
<td>MCI due to AD—high likelihood</td>
<td>Highest</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>MCI—unlikely due to AD</td>
<td>Lowest</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer’s disease; Aβ, amyloid beta peptide; PET, positron emission tomography; CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose; sMRI, structural magnetic resonance imaging.